REMARKS

Status of the Application

Claims 23-45 were pending in the application at the time the Office Action was mailed. Claims 34-38 and 45 were withdrawn. Claims 23-33 and 39-44 were rejected. No claims were allowed. Claims 23, 24, 30, 43 and 44 have been amended herein solely to expedite prosecution. Therefore, claims 23-33 and 39-44 are presently before the Examiner for consideration.

Objections

In the Office Action, claims 24 and 44 were objected to because of typographical errors. In response to the Examiner's comments, claims 24 and 44 have been amended to correct the typographical errors.

Additionally, the disclosure was objected to for failure to comply with 37 CFR 1.821 through 1.825, in particular 1.821(d), because it contains nucleotide sequences of over 10 nucleotides that are not identified by accompanying sequence identifiers. Further to the call with the Examiner on March 16, 2010, to discuss this objection, due to the high number of sequences that need to be included in a Corrected Sequence Listing, Applicants are unable to file herewith a Corrected Sequence Listing and amendments to the Specification to direct entry of corresponding sequence identifier numbers into the Specification. A Corrected Sequence Listing and corresponding amendments to the Specification in compliance with 37 CFR 1.821 through 1.825 are currently being prepared, and will be filed with a Supplemental Amendment in response to the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures and to the objections set forth in the present Office Action as soon as the Corrected Sequence Listing and amendments to the Specification are completed. Applicants thank the Examiner for the helpful and informative conversation of March 16, 2010.

Accordingly, withdrawal of these objections is respectfully requested.

Nonstatutory Double Patenting

Claims 23-33 and 39-44 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13 and 16 of U.S. Application No. 11/647,586 ("11/647,586"); claims 20-26 of U.S. Application No. 10/146,058

("10/146,058"); and claims 1-3, 5-7, 18, and 20-24 U.S. Application No. 10/581,547 ("10/581,547").

With regard to 10/146,058, applicant notes that this application was abandoned in 2007 (*i.e.* is not a pending U.S. application) and thus is not an appropriate basis for a double patenting rejection. Accordingly, withdrawal of the provisional double patenting rejection based on 10/146,058 is respectfully requested.

With regard to 11/647,586, the Office Action stated that although the allegedly conflicting claims are not identical, they are "not patentably distinct" from each other because "it would have been immediately obvious" to administer the antisense oligonucleotide as claimed in 11/647,586, to a subject as claimed in the instant application, including for subjects having skin cancer such as melanoma. 11/647,586 describes treatments for inhibiting the expression of TGF-ß and treating neurofibroma. However, the subject matter of claims 13 and 16 of 11/647,586 does not disclose or suggest a method for inhibiting the formation of metastases in a subject. At the time the instant application was filed, a person of ordinary skill in the art aware of claims 13 and 16 of 11/647,586 would not consider using the compounds of claims 13 and 16 to inhibit the formation of metastases in a subject. Therefore, it would not have been obvious to practice the instant application based on claims 13 and 16 of 11/647,586.

With regard to 10/581,547, the Office Action stated that the allegedly conflicting claims are "not patentably distinct" from each other because "it would have been immediately obvious" to administer the antisense oligonucleotides and pharmaceutical compositions thereof comprising sequences including SEQ ID NO: 30 as claimed in 10/581,547, to a subject as claimed in the instant application for subjects having melanoma. Claims 1-3, 5-7, 18 and 20-24 of 10/581,547 do not disclose or suggest use of an oligonucleotide in inhibiting the formation of metastases. At the time the instant application was filed, a person of ordinary skill in the art aware of claims 1-3, 5-7, 18 and 20-24 of 10/581,547 would not consider using the compounds of claims 1-3, 5-7, 18 and 20-24 to inhibit the formation of metastases in a subject. Therefore, it would not have been obvious to practice the instant application based on claims 1-3, 5-7, 18, and 20-24 of 10/581,547. The formation of metastases depends on an impairment of cell-cell adhesion and subsequent spreading of detached cells. In contrast, primary tumors are formed by dysregulated proliferation. Therefore, the treatment of metastases is directed to the prevention of cellular detachment and stabilization of cell-cell adhesion, but not to the decrease of tissue proliferation.

Due to these different physiological mechanisms, it is not obvious that a drug used for treatment of primary tumors is also effective in the treatment of metastases.

Accordingly, withdrawal of the provisional double patenting rejections based on 11/647,586 and 10/581,547 is respectfully requested.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 23-33 and 39-44 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the recitation "or its active derivative."

In response to the Examiner's comments, independent claims 23, 30, 43 and 44 have been amended to delete this recitation. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. §103

Claims 23-33 and 39-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,455,689 to Schlingensiepen *et al.* ("Schlingensiepen 1") and in view of U.S. Patent No. 6,120,763 to Fakhrai *et al.* ("Fakhrai"); U.S. Patent Publication No. 2004/0006030 by Monia *et al.* ("Monia"); and non-patent publication Expression of transforming growth factor-beta 2 in malignant melanoma correlates with the depth of tumor invasion: Implications for tumor progression (1994) by Reed *et al.* ("Reed"). According to the Office Action:

> It would have been obvious to use any of the anti-TGF-ß oligonucleotides disclosed by Schlingensiepen et al. to treat melanoma (and consequently inhibit metastasis) in a subject in view of the fact that Schlingensiepen et al. specifically teaches the antisense are useful for treatment of skin carcinogenesis, given that melanoma was a well recognized form of skin carcinogenesis at the time of the invention, and further given that Monia et al., Fakhrai et al., and Reed et al. taught the correlation between TGF-ß2 expression/production and malignant melanoma and specifically recommended using antisense oligonucleotides to inhibit the expression of TGF-ß and treat cancer.

Additionally, claims 23-33 and 39-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Publication No. 2007/0196269 by Schlingensiepen *et al.* ("Schlingensiepen 2") in view of Schlingensiepen 1, Fakhrai, Monia and Reed; or in the

alternative, unpatentable over U.S. Patent Publication No. 2008/0214483 by Schlingensiepen *et al.* ("Schlingensiepen 3") in view of Schlingensiepen 1, Fakhrai, Monia and Reed.

According to the Office Action:

> As a whole the prior art reasonably suggested inhibiting the expression/production of TGF-ß2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above. Accordingly, the instant methods would have been prima facie obvious at the time.

With respect to the above-described rejections, the Office Action attempts to take official notice that "[i]t would have been obvious to use any of the anti-TGF-ß oligonucleotides disclosed by Schlingensiepen et al. to treat melanoma (and consequently inhibit metastasis) in a subject in view of the fact that Schlingensiepen et al. specifically teaches the antisense are useful for treatment of skin carcinogenesis, given that melanoma was a well recognized form of skin carcinogenesis at the time of the invention, and further given that Monia et al., Fakhrai et al., and Reed et al. taught the correlation between TGF-ß2 expression/production and malignant melanoma and specifically recommended using antisense oligonucleotides to inhibit the expression of TGF-ß and treat cancer" and that "the prior art reasonably suggested inhibiting the expression/production of TGF-ß2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above. Accordingly, the instant methods would have been prima facie obvious at the time."

However, the MPEP notes that "[o]fficial notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art, are *capable of instant and unquestionable demonstration as being well-known.*" MPEP § 2144.03, p. 2100-134 (emphasis added). Such facts must be "*capable of such instant and unquestionable demonstration as to defy dispute.*" *See id.* Finally, the MPEP requires that where official notice is traversed, "the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained." MPEP § 2144.3.C.

Applicants respectfully traverse the Examiner's attempt at official notice and request that the Examiner produce supporting evidence if the rejection based on this unsupported assertion is maintained.

Prior to addressing the cited art, applicant wishes to review the claimed pharmaceutical composition as set forth in the independent claims, which recite:

23. (Currently Amended) A method for cancer treatment comprising the step of administering at least one oligonucleotide ~~or its active derivative~~ to a subject, wherein said at least one oligonucleotide ~~or its active derivative~~ inhibits the formation of metastases in said subject.

30. (Currently Amended): A method for cancer treatment comprising the step of administering at least one oligonucleotide ~~or its active derivative~~ to a subject, wherein said at least one oligonucleotide ~~or its active derivative~~ inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of prostate cancer, bladder carcinoma, colon cancer, endometrial cancer, hepatocellular carcinoma, leukemia, lymphoma, melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer or is selected from the group of melanoma, renal cancer, leukaemia, lymphoma, osteosarcoma, mesothelioma, myeloma multiple and bladder cancer.

39. (Previously Presented): A method for cancer treatment comprising the step of administering a TGF-beta 2 antagonist to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, melanoma, endometrial cancer, bladder cancer, ovarian cancer, pancreas cancer and mesothelioma.

42. (Previously Presented): A method for cancer treatment comprising the step of administering a TGF-beta 2 antagonist to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, melanoma, endometrial cancer, bladder cancer, ovarian cancer, pancreas cancer and mesothelioma.

43. (Currently Amended): A method for cancer treatment comprising the step of administering at least one oligonucleotide ~~or its active derivative~~ to a subject, wherein said at least one oligonucleotide ~~or its active derivative~~ treats metastases of said tumor.

44. (Currently Amended): A method for cancer ~~metastase~~ metastasis treatment comprising the step of administering at least one oligonucleotide ~~or its active derivative~~ to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, melanoma, bladder cancer, endometrial cancer, esophageal cancer, hepatocellular cancer, non-small-cell lung cancer, ovarian cancer, osteosarcoma, mesothelioma, renal cancer, myeloma multiple, pancreas carcinoma, leukaemia, lymphoma and soft tissue cancer.

Clearly, the claimed pharmaceutical composition and method require the at least one oligonucleotide to ***inhibit the formation of metastases*** in the subject.

Schlingensiepen 1 is drawn to the general effect of TGF-ß antisense oligonucleotides, including TGF-ß1, TGF-ß2 and TGF-ß2 antisense oligonucleotides, for the treatment of rest

tumors, for treatment of neurofibroma, malignant glioma including glioblastoma and for the treatment and prophylaxis of skin carcinogenesis as well as treatment of esophageal and gastric carcinomas. Schlingensiepen 1, col. 6, ln. 9-26. Similarly, Schlingensiepen 2 and Schlingensiepen 3 are drawn to the general effect of TGF-ß antisense oligonucleotides for the treatment and prophylaxis of tumors including, *inter alia*, skin carcinogenesis. Schlingensiepen 2, paragraphs [0001] and [0118]; Schlingensiepen 2, paragraphs [0001] and [0054].

None of Schlingensiepen 1, Schlingensiepen 2 or Schlingensiepen 3 (collectively, "Schlingensiepen references") disclose or suggest an antisense oligonucleotide that is effective in the treatment of the formation of metastases. Specifically, all three of the Schlingensiepen references fail to explicitly or implicitly disclose the inhibitory effect of antisense oligonucleotides on formation of metastases, and in particular, in the context of melanoma. The mechanism for the formation of metastases clearly differs from the mechanism for forming a primary tumor as described in the "double patenting section" (bridging paragraph p. 8 to p. 9); and a person of ordinary skill in the art would understand that each compound which is successful in inhibiting a primary tumor is not likewise efficient in inhibiting the formation of metastases or vice versa. At the time the instant application was filed, conventional wisdom would not consider using compounds to inhibit the formation of metastases in a subject based on a positive effective on a primary tumor. Therefore, it would not have been obvious to substitute the antisense oligonucleotide for the treatment of skin carcinogenesis in the Schlingensiepen references for a treatment to inhibit the formation of metastases, including in the context of melanoma. Thus the Schlingensiepen references, individually or in combination, fail to disclose or suggest the claimed pharmaceutical composition and method, wherein the at least one oligonucleotide inhibits the formation of metastases in the subject.

Fakhrai is drawn to a method of prolonging survival of a subject having a tumor, wherein the method comprises administering of genetically modified cells containing a genetic construct expressing a TGF-ß inhibitor effective in reducing or inhibiting the expression of TGF-ß. The genetically modified cells are of the same type as the subject's tumor cells. Fakhrai fails to disclose or suggest antisense oligonucleotides, which avoid the administration of cells and thus, additional negative immune reactions in the treated subject. Specifically, Fakhrai fails to disclose or suggest an antisense nucleotide of Seq. ID No. 30 or provide any information on the inhibition of the formation of metastases with the antisense oligonucleotide.

Monia is drawn to numerous modifications of antisense oligonucleotides for the treatment of, *inter alia*, several forms of cancer. Monia, paragraph [0012]. However, Monia fails to disclose or suggest an antisense oligonucleotide such as that of Seq. ID. No. 30, which is suitable to be used as a method for treating melanoma or for inhibiting the formation of metastases. As discussed above, a positive effect of a compound on a primary tumor does not indicate the same effect for inhibiting the formation of metastases.

Reed is drawn to expression of TGF-ß2 in metastatic melanomas in vitro. However, this result was not confirmed in vivo, as all lesions of melanoma in situ were TGF-ß2 negative. *See* Reed, p. 99, col. 2, second paragraph; p. 100, Fig. 1d. Reed discloses that the use of a TGF-ß antisense nucleotide is not reliable for inhibiting the formation of metastases. As such, Reed teaches away from the claimed pharmaceutical composition and method.

Therefore, Fakhrai, Monia and Reed fail to correct the deficiencies of the Schlingensiepen references, and the combination of all of these references fails to disclose or even suggest use of the claimed oligonucleotides for inhibiting formation of metastases in a subject.

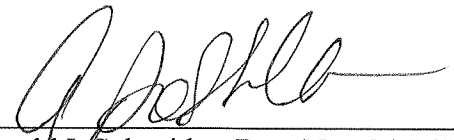
For at least the foregoing reasons, the cited references in combination fail to teach each and every claim limitation of the instant application. Accordingly, withdrawal of these rejections is respectfully requested.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

A Request for a Retroactive Extension of Time is filed herewith. A credit card payment is made herewith for the required fee. However, the Commissioner for Patents and Trademarks is hereby authorized to charge any underpayment of fees or credit any overpayment of fees to Deposit Account No. 14-1437.

Respectfully submitted,



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